Appendix

Equations and Parameters for Model Simulations

Ca^{2+} Subspace Model
As in Zhang et al., Biophys. J. 84(5):2852–2870, Fig. 10, except as noted.
(To be posted online but not included in paper.)

Units:

Conductances	pS
Currents	fA
Ca concentrations	μM
Time	ms
Capacitance	fF

Differential Equations (deterministic):

$$C_m \frac{dv}{dt} = -I_{\mathrm{Ca}} - I_{\mathrm{Kv}} - I_{\mathrm{KATP}} - I_{\mathrm{KCa}} - I_{\mathrm{Leak}} \tag{1}$$

$$\frac{dn}{dt} = \frac{n_\infty(v) - n}{\tau_n} \tag{2}$$

$$\frac{dc}{dt} = f_{\mathrm{CYT}}\left(-\alpha I_{\mathrm{Ca}} - J_{\mathrm{PMCA}} - J_{\mathrm{SERCA}} + J_{\mathrm{X}}\right) \tag{3}$$

$$\frac{dc_{\mathrm{ER}}}{dt} = f_{\mathrm{ER}}\left(\frac{V_{\mathrm{CYT}}}{V_{\mathrm{ER}}} J_{\mathrm{SERCA}} - J_{\mathrm{RELEASE}}\right) \tag{4}$$

$$\frac{dc_{\mathrm{SS}}}{dt} = f_{\mathrm{SS}}\left(\frac{V_{\mathrm{ER}}}{V_{\mathrm{SS}}} J_{\mathrm{RELEASE}} - \frac{V_{\mathrm{CYT}}}{V_{\mathrm{SS}}} J_{\mathrm{X}}\right) \tag{5}$$

Initial Conditions:

V	-21.366
n	0.14168
c	0.0516
c_{ER}	193.02
c_{SS}	0.1851

Ionic Currents:

$$
\begin{aligned}
I_{\mathrm{Ca}} &= g_{\mathrm{Ca}} m_{\infty}(v)(v - v_{\mathrm{Ca}}) && (6)\\
I_{\mathrm{KCa}} &= g_{\mathrm{KCa}} \omega (v - v_{\mathrm{K}}) && (7)\\
I_{\mathrm{KATP}} &= g_{\mathrm{KATP}} (v - v_{\mathrm{K}}) && (8)\\
I_{\mathrm{Kv}} &= g_{\mathrm{K}} n (v - v_{\mathrm{K}}) && (9)\\
I_{\mathrm{Leak}} &= g_{\mathrm{Leak}} (v - v_{\mathrm{Leak}}) && (10)
\end{aligned}
$$

where:

$$
\begin{aligned}
n_{\infty}(v) &= \frac{1}{1 + \exp((v_n - v)/s_n)} && (11)\\
m_{\infty}(v) &= \frac{1}{1 + \exp((v_m - v)/s_m)} && (12)\\
\omega(c_{\mathrm{SS}}) &= \frac{c_{\mathrm{S}S}^q}{c_{\mathrm{S}S}^q + K_d^q} && (13)
\end{aligned}
$$

Parameters:

for $I_{\mathrm{K}v}$:

g_{Kv}	2500
v_{K}	-70
v_n	-15
s_n	5.6
τ_n	10.8

for I_{Ca}:

g_{Ca}	1450
v_{Ca}	30
v_m	-13
s_m	8

for I_{KCa}:

g_{KCa}	1200
K_d	0.7
q	8

for I_{Leak}:

g_{Leak}	14
v_{Leak}	-30

for I_{KATP}:

g_{KATP}	60

Calcium fluxes: (μM ms^{-1})

$$\begin{aligned}
J_{\mathrm{PMCA}} &= k_{\mathrm{PMCA}}\, c && (14)\\
J_{\mathrm{SERCA}} &= k_{\mathrm{SERCA}}\, c && (15)\\
J_{\mathrm{RELEASE}} &= p_{\mathrm{ER}}\, (c_{\mathrm{ER}} - c_{\mathrm{SS}}) && (16)\\
J_{\mathrm{X}} &= p_{\mathrm{X}}\, (c_{\mathrm{SS}} - c) && (17)
\end{aligned}$$

with rates: (ms^{-1})

p_{X}	0.025
p_{ER}	0.001
k_{PMCA}	0.2
k_{SERCA}	0.2

and buffer parameters*:

f_{CYT}	0.01
f_{ER}	0.005
f_{SS}	0.04

*(dimensionless fraction of calcium that is free in each compartment)

Volume ratios:

$$\frac{V_{\mathrm{ER}}}{V_{\mathrm{SS}}} = 0.1 \tag{18}$$

$$\frac{V_{\mathrm{CYT}}}{V_{\mathrm{SS}}} = 2.5 \tag{19}$$

$$\frac{V_{\mathrm{CYT}}}{V_{\mathrm{ER}}} = 25.0 \tag{20}$$

$$\frac{V_{\mathrm{SS}}}{V_{\mathrm{CYT}}} = 0.4 \tag{21}$$

Miscellaneous:

Unit Conversion for ICa (converts fA to μM ms^{-1}):

$$\alpha = \frac{1}{2FV_{\mathrm{CYT}}} = 4.5 \times 10^{-6} \mu\mathrm{M\ fA}^{-1}\ \mathrm{ms}^{-1}$$

Here 2 is the valence of calcium; F is Faraday's constant; and V_{CYT} is the volume of the cytosol.
Capacitance: $C_m = 5300$

Output function to report the free cytosolic Ca^{2+} that would be reported by fura imaging:

$$c_{\mathrm{AVG}} = \frac{V_{\mathrm{SS}} c_{\mathrm{SS}} + V_{\mathrm{CYT}} c}{V_{\mathrm{SS}} + V_{\mathrm{CYT}}}$$

Noise:

For simulations including channel noise, I_{KATP} is redefined as

$$I_{\mathrm{KATP}} = \bar{g}_{\mathrm{KATP}} s (V - V_{\mathrm{K}})$$

where s satisfies the stochastic differential equation (SDE; (Kloeden, Platen, and Schurz, 1997):

$$ds = [\alpha(1-s) - \beta s]dt + \sigma dW.$$

The magnitude of the noise term is

$$\sigma = \left\{ [\alpha(1-s) + \beta s] \, / \, [\tau N_{\mathrm{KATP}}] \right\}^{1/2},$$

with parameters $\alpha = 1$ msec^{-1}, $\tau = 100$ msec, $N_{\mathrm{KATP}} = 500$, and β chosen such that the deterministic steady state,

$$\frac{\alpha}{\alpha + \beta} = 0.20.$$

Combined with $g_{\mathrm{KATP}} = 300$ pS, this makes the mean value of $g_{\mathrm{KATP}} = 60$ pS, as stated in the table for I_{KATP} above. This makes the single-channel conductance much smaller than it is in reality, suggesting that the model is overly sensitive to g_{KATP}. Nonetheless, this is a convenient locus for illustrating the effects of noise.

Multi-Cell (Islet) Simulations:

All equations and parameters above are the same as used in Zhang et al, Fig. 10, except that dynamic clamp current was not applied. In addition, some simulations in the present paper involved many coupled cells to represent an intact islet. Cells were indexed by i and arranged in a $10 \times 10 \times 10$ cube. A coupling term was added to the V equation as follows:

$$\begin{aligned} C_m \frac{dv_i}{dt} &= -I_{\mathrm{Ca}}(v_i) - I_{\mathrm{Kv}}(v_i, n_i) - I_{\mathrm{KATP}}(v_i, s_i) - I_{\mathrm{KCa}}(v_i, c_i) - I_{\mathrm{Leak}}(v_i) \\ &\quad - g_c \sum_{j \in \Omega} (v_i - v_j) \end{aligned} \tag{22}$$

where Ω is the set of neighbors, which consists of 3 – 6 cells depending on whether the cell i is a corner, edge, face, or interior cell. Coupling conductance $g_c = 800$ pS per connection (total coupling conductance for a cell ranged from 2400 – 4800 pS). Note that each cell had an independent channel noise variable, s_i. Initial conditions were randomized by a uniformly distributed 10% perturbation to avoid artifactual synchronization and the first 300 seconds of simulation time were discarded to eliminate transients.

Heterogeneity

Heterogeneity is introduced by randomly distributing g_{Ca} around its mean value of 1450 pS. A normal distribution with variance 10 pS was used for Fig. 2 ("Synchrony Model"). This value was suitable for desynchronizing the individual cells when uncoupled from the islet while preserving their ability to exhibit medium to slow bursting. For Fig. 3 ("Channel Sharing Model"), the variance was 20 pS. With this value the model could represent most of the range of single cell behaviors observed experimentally in our previous studies (Kinard et al, 1999; Zhang et al, 2003), in which more than 90% of the cells were spikers or fast bursters.

Methods

The stochastic equations were integrated by the Euler-Maruyama method:

$$s_{n+1} = s_n + \Delta t(\alpha(1 - s_n) - \beta s_n) + \sigma_n \Delta W_n \tag{23}$$

where $\{\Delta W_n\}$ is a set of independent random variables distributed as $N(0, \Delta t)$. Normal random variables were generated using the program drnor.f, available as module DRNOR from the Guide to Available Mathematical Software (`http://gams.nist.gov`).

The time step was 0.1 msec which was deemed to be adequate based on comparison with higher order, variable time-step methods applied to the deterministic case. In addition, values of ΔW_n that caused s_{n+1} to go outside the interval $[0, 1]$ were discarded and a new random variable chosen until the interval constraint was satisfied. See Fox, 1997.

Programs were written in fortran and compiled using the GNU g77 compiler under Red Hat Linux 7.3. Xpp files giving equivalent results for the single-cell cases are posted at: `http://mrb.niddk.nih.gov/sherman`.